REMARKS

Status of the Claims

Claims 6-9 are pending in this application. In the present response, claims 1-5 and 10-22 have been canceled without prejudice to or disclaimer of the subject matter therein. Claim 6 has been amended as described elsewhere herein. Support for this amendment is set forth in the Remarks, below, or can found in the original claims as filed. Thus, no new matter has been added by way of amendment.

The Examiner's comments are addressed below in the order set forth in the Office Action.

Review and Reconsideration of the Restriction Requirement

Applicants wish to thank the Examiner for withdrawing SEQ ID NO:10 from Groups C and D and rejoining it with Groups A and B, namely claims 1-5 and 14-16, SEQ ID NOS:2, 10, and 35.

The Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claims 6-9 have been rejected as indefinite under 35 U.S.C. § 112 for reciting the term "CASB7439" in claim 6. Specifically, the term is objected to as indefinite on the reasoning that it is a "laboratory designation." Solely to expedite prosecution, Applicants have amended claim 6 to no longer recite the term CASB7439. Support for the amendment can be found within the specification at paragraph [0089]. Dependent claims 7-9 never recited the term. Thus, the concerns expressed in the rejection are thereby alleviated. Applicants respectfully request that the rejection be withdrawn.

The Rejections Under 35 U.S.C. § 112, 1st ¶, Written Description, Should be Withdrawn

Claims 6-9 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. This rejection is respectfully traversed.

As an initial matter, the rejection has specifically founded the rejection on the recitation of "inducing an immunoresponse to **CASB7439**" within claim 6. For the reasons stated above, the claim has been amended to recite "inducing an immunoresponse to ASCL2." Thus, the concerns expressed in the rejection over the recitation "CASB7439" are alleviated.

In any case, the rejection states that the specification does not provide a written description for the genus of molecules recited in the claims. The rejection expressly relies on legal precedent related to claiming a genus of novel compounds, stating "[t]he specification also fails to describe CASB7439 protein, by the standards shown in the example in *Lilly*." See page 6 the Office Action. While the rejection has stated the correct legal standard for novel compositions, this is not the correct standard in the present case for reasons explained in the following paragraph.

Subsequent to the publication of the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1 'Written Description' Requirement," 66 Fed. Reg. 1099 (January 5, 2001), the Federal Circuit clarified the written description standards applicable to the examination of subject matter in which a *known* composition is recited in the claims. *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (CA FC 2003). The court explained that "[w]e held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself — not merely a recitation of its function or a reference to a potential method for isolating it… …*Eli Lilly*…[is] inapposite to this case *because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily*

miscomprehend." As in the *Amgen* appeal, Applicants are not claiming compositions made from new or unknown biological materials. Rather, the currently pending claims are drawn to methods involving fragments comprising epitopes identified by Applicants of a known polypeptide, namely SEQ ID NO:2.

At the time of filing, the genus of ASCL2 polypeptides had already been described in the scientific literature and exemplified by many homologues; much was known about its structure, including its sequence and evolutionarily conserved regions. See Alders *et al*. (1997) *Hum. Molec. Genet.* 6: 859-867; Johnson *et al*. (1990) *Nature* 346, 858–861. Further, the specification provides guidance regarding the structure of epitopes of CASB7439:

> [0054] Peptide fragments incorporating an epitope of CASB7439 typically will comprise at least 7, or 9 or 10 contiguous amino acids from SEQ ID NO:2. Epitopes also include those shown in SEQ ID NO:16 to SEQ ID NO:33.
>
> [0055] Peptides that incorporate these epitopes form one aspect of the present invention.
>
> . . . .

See the specification, ¶¶ [0054] and [0055]. The specification contains further guidance regarding epitopes predicted to behave in a particular class restricted manner, as well as experimental work carried out with exemplary epitopes. See the Examples, particularly Examples 9-12 and 17. Given the knowledge in the art of the structure of ASCL2 and the guidance provided within the specification, the ordinarily skilled artisan would easily comprehend the claimed subject matter. The written description standard is therefore satisfied. Applicants respectfully request that the rejection of claims 6-9 be withdrawn.

The Claims Rejections Under 35 U.S.C. § 112, 1st ¶, Should Be Withdrawn

Claims 6-9 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. The rejection is founded on two main lines of reasoning: first, that Applicants must demonstrate successful cancer treatment to

demonstrate enablement and, second, that cancer vaccines are so inherently unpredictable that one of skill in the art would not be able to make or use Applicants' claimed subject matter. Applicants respectfully traverse for two reasons:

(1) The rejection's conclusion that cancer vaccines and/or therapies are so inherently unpredicatable such that one of skill in the art would not be able to utilize a peptide fragment of SEQ ID NO:2 is not supported by the record; and

(2) The rejection improperly construes the claims to require that the recited method steps successfully treat cancer.

These two bases for traversal are explained in the following two Sections.

Section (1)

The rejection contends that, in general, those of skill in the art express reservations about cancer vaccines. In support, many scientific publications are cited. However, almost half of the references cited in this portion of the Office Action are from 1995 or earlier. Applicants submit that the scientific publications by Smith (1994) *Clin. Immunol.* 41:841-9; Boone (1992) *Adv. Can. Res.* 58:177-210; Ezzell (1995) *J. NIH Res.* 7:46-9; and Spitler (1995) *Cancer Biotherapy* 10:1-3 are all irrelevant to the inquiry of whether the presently claimed subject matter is enabled because they do not represent the current views of the skilled artisan.

Applicants draw the Office's attention to more recent reviews such as Rosenberg *et al*. (2004) *Nat. Med*. 10:909-915, which reports on cancer studies involving MART-1, gp-100, tyrosinase, TRP-2, NY-ESO-1, MAGE-12, Her2/neu, and telomerase proteins. Tsuruma (2005) *Vaccines & Antibodies* 5:799-807 reports on studies involving genes highly expressed in colorectal cancer. An even more recent report suggests a spectrum of appropriate endpoints by which to measure efficacy of cancer vaccines. See Hoos *et al*. (2007) *J. Immunother.*

30:1-15. Applicants have submitted each of these references for consideration by the Office. A review of the references cited on the preceding page will reveal that methods involving immunogenic fragments of polypeptides, like those recited in the claims, are useful as an adjuvant to other therapeutic modalities ranging from chemotherapy to surgical approaches. Moreover, immunogenic fragments are useful in non-vaccine settings, such as adoptive immunity.

The rejection also questions whether Applicants' recited method steps could successfully treat cancer. For support, it cites White *et al.* (2001) *Ann. Rev. Med.* 52:125-45 for the principle that repeat dosing with antigen *may* become ineffective due to antigen internalization or down-regulation. Applicants emphasize that their claims contain no requirement that the recited method successfully treats cancer by itself. Rather, the claims recite a method of inducing an immune response. [This point is dealt with in Section (2), below.] Regardless of the discussion in White *et al.* about the effects of repeat dosing, the reference is irrelevant to whether one could induce an immunoresponse to ASCL2 by administering a peptide fragment of SEQ ID NO:2.

The rejection also cites Kirkin *et al.* (1998) *APMIS*106:665-79 for its discussion of research related to MAGE-A1 and –A3 peptide induced immunoresponse. Specifically, the rejection states that only one peptide discussed in the reference demonstrated anti-tumor activity and that Kirkin *et al.* described the MAGE peptide antigens as having low immunogenicity. Extrapolating from Kirkin *et al.*, the rejection questions whether one could use the peptide-based method recited in Applicants' claims to successfully treat cancer. However, Kirkin *et al.* actually supports a conclusion that a peptide approach is viable. And more recent references provide further support for a conclusion that a peptide approach is viable. See Marchand *et al.* (1999) *Int. J. Cancer* 80:219-230, which states in its abstract:

> Thirty-nine tumor-bearing patients with metastatic melanoma were treated with 3 subcutaneous injections of the MAGE-3.A1 peptide at monthly intervals. No significant toxicity was observed. Of the 25 patients

> who received the complete treatment, 7 displayed significant tumor regressions. All but one of these regressions involved cutaneous metastases. Three regressions were complete and 2 of these led to a disease-free state, which persisted for more than 2 years after the beginning of treatment. No evidence for a cytolytic T lymphocyte (CTL) response was found in the blood of the 4 patients who were analyzed, including 2 who displayed complete tumor regression. Our results suggest that injection of the MAGE-3.A1 peptide induced tumor regression in a significant number of the patients, even though no massive CTL response was produced.

Applicants have submitted the Marchand *et al*. reference for consideration by the Office. (Applicants again emphasize that their claims contain no requirement that the recited method successfully treats cancer by itself, as will be discussed in Section 2, below.)

Gaiger (2000) *Blood* 96:1480-9 is cited in the rejection for its report that WT-1 peptides, although immunogenic, did not show any effect on WT-1 cancer growth *in vivo*. However, recent studies contradict Gaiger *et al.* Other researchers have demonstrated that peptide fragments of WT-1 *are* immunogenic *and do* affect cancer growth *in vivo*. See Oka *et al*. (2004) *PNAS* 101:13885-13890. For the reader's convenience, Applicants have reproduced portions of the abstract:

> Here, we report the outcome of a phase I clinical study of WT1 peptide-based immunotherapy for patients with breast or lung cancer, myelodysplastic syndrome, or acute myeloid leukemia. Patients were intradermally injected with an HLA-A*2402-restricted, natural, or modified 9-mer WT1 peptide emulsified with Montanide ISA51 adjuvant at 0.3, 1.0, or 3.0 mg per body at 2-week intervals, with toxicity and clinical and immunological responses as the principal endpoints.
>
> . . . .
>
> Twelve of the 20 patients for whom the efficacy of WT1 vaccination could be assessed showed clinical responses such as reduction in leukemic blast cells or tumor sizes and/or tumor markers. A clear correlation was observed between an increase in the frequencies of WT1-specific cytotoxic T lymphocytes after WT1 vaccination and clinical responses. It was therefore demonstrated that WT1 vaccination could induce WT1-

> specific cytotoxic T lymphocytes and result in cancer regression without damage to normal tissues.

Applicants have submitted the Oka *et al*. reference for consideration by the Office.

Moreover, those of skill in the art conclude that the sort of direct effect upon cancer growth discussed by Gaiger *et al*. is an inappropriately restrictive endpoint by which to assess a vaccine, let alone a method of inducing an immunoresponse. For instance, a panel of scientists from academia and industry formulated guidelines by which to assess vaccines, published in a report titled "A Clinical Development Paradigm for Cancer Vaccines and Related Biologics." The report states:

> It is currently assumed, immune effects induced by vaccines may less likely reduce bulk of tumor but more likely target small quantities of cancer cells or minimal residual disease (MRD). Thus, single-arm trials using historical control data as the comparator and *short-term end points like tumor response may not reflect the full extent of the product* to induce clinical activity. Instead, end points in early trials with cancer vaccines should reflect parameters of biologic activity.

Hoos *et al*. (2007) *J. Immunother.* 30:1-15 (italics added.) Thus, serious scientific questions may be raised about using tumor mass as an endpoint to evaluate WT-1 peptides. Applicants have submitted the Hoos *et al*. reference for consideration by the Office.

The rejection also relies upon Roitt *et al*. (1998) *Immunology*, 4th ed., Mosby, London, p. 7.7-7.8 for the principle that it is possible to produce antibodies to almost any part of a polypeptide, but that (1) an immune response is generally triggered by only specific areas of the antigen; (2) antibodies only bind to certain antigenic regions of a polypeptide; and (3) only a minority of peptide fragments from a protein are able to bind to a particular MHC molecule. None of points (1)-(3) support the rejection. Applicants have disclosed specific epitopes of SEQ ID NO:2. See specific data as described in Section (2), below. Applicants have therefore provided guidance to those of skill in the art regarding

epitopes likely to engender an immunological response, bind antibody, and/or bind MHC molecules. In other words, the specification does provide guidance related to each of points (1)-(3) of Roitt *et al*. With this guidance, one of skill in the art could practice the claimed invention without undue experimentation.

Considering all of the references, the record now refutes the rejection's conclusion Applicants' claimed method is so unpredictable that one of skill in the art could not practice it without undue experimentation. For this reason alone, the rejection has not established nonenablement and it should be withdrawn.

Section (2)

The rejection should also be withdrawn for an additional reason. Specifically, the rejection construes the claims as if they require the recited fragment to successfully treat cancer by itself. First, the rejection reasons that "[i]t is noted that a method for inducing an immune response to CASB7439 encompasses a method for **treating cancer**. Further a method for inducing an immune response, using a peptide fragment of SEQ ID NO:2, as claimed in claims 6, 8, 9, encompasses a method for treating cancer…." See the Office Action mailed 27 Oct 2006, page 7 (emphasis added). Then the rejection concludes:

> "The specification however does not have any objective evidence of ***successful treatment of cancer*** by CTLs or antibodies induced by administration of the peptide of SEQ ID NO:25…[or] that sufficient and high affinity CTLs or antibodies are produced in cancer patients with cancer burden, where the problem of cancer tolerance, with suppression of CTLs and/or antibody production, is common."

See the Office Action, page 12, first full paragraph (emphasis added). However, pending claim 6—reproduced in the following text for the reader's convenience—does not and never did contain any "successful treatment" limitation:

> 6. A method of inducing an immunoresponse to ASCL2 in a human or non-human animal comprising administering a peptide fragment of SEQ ID NO:2 to the human or non-human animal, said peptide fragment comprising an epitope of SEQ ID NO:2.

None of the currently examined dependent claims recite "treating cancer," "cancer treatment," or the like.

Notwithstanding that Applicants' claims recite a method of inducing an immunoresponse, the rejection is formulated as if the claims recite a step of successfully treating cancer. This is not proper. Applicants understand that it is unlikely that one could successfully treat cancer using a polypeptide fragment without inducing an immune response, but it does not follow that one must effectively treat cancer to enable induction of an immunoresponse to a polypeptide fragment.

It is elemental that a rejection must be based upon a correct reading of the claims. Indeed, the MPEP cautions that "Office personnel should also be especially careful not to read into a claim unclaimed results, limitations or embodiments of an invention." See MPEP § 2107.02 *citing Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961). The present rejection should be withdrawn because it is based upon the incorrect assumption that the claims require successful cancer treatment.

To the extent the rejection is based upon the reasoning that the claims encompasses methods that *might potentially* result in the outcome of treating cancer, the rejection is improper as well. The pertinent inquiry is "whether the disclosure presented is enabling for the claimed subject matter." *See In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)(enablement inquiry is whether one skilled in the art, after reading the patent disclosure, could practice the claimed subject matter without undue experimentation). Despite the actual elements of Applicants' claims, the rejection sets forth the following findings under the *Wands* enablement inquiry:

> "The breadth of the claims is broad. The claims encompass a method for *treating cancer*…."

. . . .

> "The nature of the invention is complex, *comprising cancer treatment* using peptides for activating specific cytotoxic T cells, or for producing antibodies that could kill cancer cells in cancer patients."

See the Office Action, page 7 (italics added). Contrary to the claim construction evident in the Office Action, Applicants have claimed a method of inducing an immunoresponse to ASCL2 and the inquiry should be focused upon this subject matter, not the *potential* outcome of the claimed method. The present rejection should be withdrawn because the enablement analysis is founded on an improper reading of the claims.

In addition, the rejection is founded on suppositions that are refuted by the record. For instance, the rejection states that

> [o]ne cannot predict that SEQ ID NO:25 or any fragments of SEQ ID NO:2 could be used for producing CTLs or antibodies specific for SEQ ID NO:2, effective for cancer treatment because 1) cancer treatment is unpredictable and 2) one cannot predict that SEQ ID NO:2 is adequately immunogenic and exposed in sufficient quantities on the surface of malignant cells in vivo such that CTLs could recognize and lyse said malignant cells.

The rejection's contention that "cancer treatment is unpredictable" has been dealt with in Section 1, above, and will not be further discussed here.

Regarding the doubts expressed regarding the immunogenicity of SEQ ID NO:2, this reasoning is based on the twin suppositions that (i) fragments of SEQ ID NO:2 would be insufficiently immunogenic *by themselves* to be immunogenic and (ii) that ASCL2 may not be sufficiently expressed in malignant cells to provide an effective target. In the following paragraphs, Applicants will deal with each of these two suppositions independently.

Immunogenicity. To support the contention that "one cannot predict that SEQ ID NO:2 is adequately immunogenic," the rejection presumes that a fragment of SEQ ID NO:2 must be sufficiently immunogenic *by itself* to be considered immunogenic. But nothing in Applicants' claims require that a

particular species of fragment be utilized by itself, or that the fragments be used by themselves. The rejection ignores the open "comprising" transition of the claim which indicates that one species of peptide fragment may optionally be utilized with other components to induce an immunoresponse. Indeed, the dependent claims recite a peptide fragment of SEQ ID NO:2 in conjunction with other elements, such as a fusion partner (claim 8) or an adjuvant (claim 9). Those of skill in the art would also understand that a peptide cocktail comprising more than one species of fragment may be used.

Moreover, Applicants have provided evidence to support a conclusion that fragments of SEQ ID NO:2 that comprise one of the disclosed epitopes would be immunogenic. In Example 11, Applicants provide immunohistochemistry (IHC) data showing high levels of anti-CASB7439 immunoreactivity in colon cancer and very low levels in normal colon. See paragraph [0369] of the specification. Specifically, anti-CASB7439 immunoreactivity was localized to the cytoplasm and associated with the plasma membrane of the cells. See Figures 7 and 8.

In addition, the Examples present *in vitro* data showing that several peptides which overlap the epitope of SEQ ID NO:25 *are* specifically recognized by CD4+T cells. See Example 10, "CASB7439 Specific Cellular Immune Response," especially paragraph [0365] of the specification. In the Example, cells were assayed for proliferation (3H-Thy) as well as IFN-γ. See paragraph [0360] of the specification. In sum, this evidence supports a conclusion that the fragments recited in the claimed methods can be used to induce a CD4+ immunoresponse, as assayed *in vitro* by cellular proliferation as well as IFN-γ response. (See Hoos *et al.*, page 7, paragraph spanning columns 1 & 2, discussing the use of cytokine assays as a marker for immune response.) The rejection's contention that ASCL2 would be insufficiently immunogenic is not supported by the record.

Insufficient Expression. The rejection's second supposition is that ASCL2 may not be present in "sufficient quantities on the surface of malignant cells in

vivo…." In particular, the rejection contends that "variants of SEQ ID NO:2 may not be expressed on colon cancer cells, to be recognized and lysed by CTLs, because it is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type." Office Action paragraph spanning pages 10-11 (emphasis added). To the extent the rejection is based upon the supposition that SEQ ID NO:2 or other isoforms of ASCL2 may not be expressed on colon cancer cells, or that they may be expressed at low levels, Applicants have disclosed experimental data specific to the polypeptide at issue in the present case. In particular, Applicants have disclosed IHC observations that anti-CASB7439 immunoreactivity is at a high level in colon cancer and at a very low level in normal colon. See Figures 7 and 8.

Others have now confirmed Applicants' findings by showing that ASCL2 is highly expressed in colon cancer at the nucleic acid level:

> Using oligonucleotide microarrays we identified ascl2 as a gene significantly upregulated in colorectal adenocarcinomas (n=36 cancers, n=16 normals; 15-fold, P<0.0001). This finding was confirmed by quantitative reverse transcriptase (RT)–PCR on large intestinal cancers (n=29 cancers, n=16 normals; 10-fold, P<0.0001). In situ hybridization for ascl2 demonstrated expression at the base of small and large intestinal crypts (n=304), but in no other normal tissues excepting placenta. By in situ hybridization, 52–71% of colorectal adenomas (n=187), 50–73% of large (n=327) and 33–64% of small intestinal adenocarcinomas (n=124) were positive for ascl2 expression. Upregulation of murine ascl2 was also observed using oligonucleotide microarrays, quantitative RT–PCR and in situ hybridization on apcmin/+ and apc1638N/+ smad4-/+ tumours.

Jubb *et al*. (2006) *Oncogene,* 25:3445–3457. Notably, Jubb *et al*. confirmed the neoplastic upregulation of human *and murine variants* of ASCL2. Thus, the rejection's concern over variants is alleviated. (Applicants have submitted Jubb *et al*. by information disclosure dated August 2006, but will be happy to submit a courtesy copy upon request.)

Although the rejection cites scientific references to Schmid and Conner in support of the general proposition that polypeptide variants may be expressed at different levels, these references discuss gene products other than ASCL2 and are not germane here. Jubb *et al*. is a more relevant reference to the question of whether ASCL2 is expressed in colon cancer. Jubb *et al*. confirms that mouse and human variants are expressed in neoplastic colon tissue. To carry its burden of demonstrating nonenablement, the rejection must provide evidence specific to the ASCL2 polypeptide sufficient to rebut the combination of Applicants' experimental data and the Jubb *et al*. reference. The rejection's contention that ASCL2 would be insufficiently expressed is overcome by the evidence of record.

In its closing paragraphs, the rejection makes it absolutely clear that Applicants are being held to a standard in which enablement is equated with successful cancer treatment. It states: "The specification however does not have any objective evidence of ***successful treatment of cancer*** by CTLs or antibodies induced by administration of the peptide of SEQ ID NO:25…[or] that sufficient and high affinity CTLs or antibodies are produced in cancer patients with cancer burden, where the problem of cancer tolerance, with suppression of CTLs and/or antibody production, is common." See the Office Action, page 12, first full paragraph (emphasis added). A requirement that Applicants demonstrate a successful cancer treatment to the same degree that might be found in clinical trials would be wholly inappropriate even if Applicants' claims included a cancer treatment element: It is well-settled that the statutory standards for enablement are in no way related to (and generally much lower than) those used to assess efficacy in clinical trials.

For all of the reasons stated above, the Office Action has not demonstrated that it would require undue experimentation for one of skill in the art to practice the claimed subject matter. It is the Office's burden to establish a prima facie case of nonenablement by objective evidence and findings under the

appropriate statutory standard. This has not been done here. The rejection of claims 6-9 should be withdrawn.

CONCLUSION

In view of the remarks herein above, Applicants respectfully submit that the rejection of claims 6-9 is overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

/Eric J. Kron/
Eric J. Kron
Attorney for Applicants
Registration No. 45,941

Date: 15 Feb 2007
GlaxoSmithKline
Five Moore Drive, PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone: (919) 483-8961
Facsimile: (919) 483-7988